

18. (Amended) The method of claim 15 wherein the analysis of step (d) is a promoter activation assay.

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REMARKS

The October 2, 2002 Office Action has rejected claims 15, 17 and 18 under 35 U.S.C. § 112, second paragraph and claims 15, 16 and 19 under 35 U.S.C. § 103. The Office Action has also requested an amendment and corrected drawings. In light of the amendments above and the arguments below, Applicants respectfully request reconsideration.

Drawings

Applicants have enclosed corrected drawings.

Specification

Applicants have corrected the typographical error of "ranilla" to "renilla."

§ 112

Claims 15, 17 and 18 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner has rejected claim 12 on the grounds that it is not clear what is meant by "whereby an operable factor will link the site." Applicants have reworded the claim to clarify that the factors link the

binding sites and the sites are in this state at the time of the addition of the candidate molecule.

The Examiner questions the language "the candidate molecule inhibits protein:protein linking . . . unable to mediate linking." Applicants have now amended claim 15 to clarify that it is the interaction within the looping/linking factor that is disrupted.

Applicants have now amended the preamble to claim 15 to be consistent with the last step of claim 15.

Claims 17 and 18 have been amended to recite "the analysis of step (d)."

§ 103

The Examiner has rejected claims 15, 16 and 19 under 35 U.S.C. § 103(a) as being unpatentable over Mackey, et al. in view of Becker, et al.

Applicants disagree with the Examiner's characterization of the combination of Mackey, et al. and Becker, et al. Applicants have asserted in previous responses that an *in vitro* showing of inhibition (Mackey, et al.) is not determinative of *in vivo* demonstration because in an *in vivo* situation the DNA in the nucleus is not naked but is covered with DNA associated proteins, such as histones. Applicants submit a copy of the Declaration of Inventor Dr. William M. Sugden (submitted

previously). Dr. Sugden characterizes Mackey, et al. as demonstrating that

"EBNA-1 encodes multiple domains which when fused to a protein that binds DNA site-specifically links those bound DNAs *in vitro*. This study does not measure DNA-linking *in vivo* in the presence and absence of candidate inhibitors nor is it certain that such linking could occur. DNAs *in vivo* are not naked nor are they freely diffusible. Rather, DNAs within nuclei in cells are likely to be bound by a complex array of proteins to form chromatin and to be compartmentalized such that local concentrations of proteins with which they interact may not be uniform."

At paragraph 6, Dr. Sugden goes on to say that "only genetic studies which can alter a protein structure in cells . . . could address the putative role of EBNA-1's linking domains"

This genetic analysis is provided by the present invention. Applicants resubmit this Declaration of Dr. Sugden for the Examiner's review.

The addition of Becker, et al. as disclosing a cell based assay does not change Applicants' analysis. The Examiner cites Becker, et al. as providing "the EBV cell inhibition assay" Even granted that one of ordinary skill in the art "would have been motivated to utilize the cell based format of Becker, et al. for the molecular format of Mackey, et al." Applicants assert that it would not have been apparent that this assay would be successful. The Becker, et al. reference

discloses a determination of viral replication or inhibition but does not speak to the ability to detect perturbations in the particular looping/linking factors upon which Applicants have chosen to focus. Becker's study deals with an antibiotic inhibiting the lytic cycle of EBV. There is no reason to think that EBNA1 contributes to the lytic cycle of EBV. The present invention pertains to the latent cycle of the virus during which, by definition, no progeny virus is synthesized and EBNA1 is essential to maintain the viral replicon in the proliferating cell.

Applicants note that claims 17 and 18 are not rejected under 35 U.S.C. § 103(a).

Applicants respectfully request reconsideration. Applicants have enclosed a Petition and Fee for One Month's Extension of Time. No other fees are believed necessary to enter this response. However, if any fees are necessary, please charge Deposit Account 17-0055.

Respectfully submitted,

William M. Sugden, et al.

January 31, 2003

By: 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: William M. Sugden, et al.
Serial No.: 09/808,517
Filed: March 14, 2001
For: INHIBITION OF VIRAL GENE ACTIVITIES
Group Art Unit: 1648
Examiner: U. Winkler

MARKED UP COPY OF THE CLAIMS

15. (Amended) A method of screening candidate molecules for the ability to disrupt viral looping/linking factors [viral replication inhibitors and viral transcription inhibitors] comprising:

(a) adding a candidate molecule to a mammalian cell culture;

(b) providing a control mammalian cell culture without the candidate molecule, wherein the cell cultures of both (a) and (b) comprise viral looping/linking factors, wherein the factors comprise DNA-binding proteins that can self-associate, and nucleic acid molecules comprising at least two binding sites for the factors, [whereby an operable] wherein the sites are linked by a looping/linking factor [will link the sites];

(c) allowing said candidate molecule to interact with the viral looping/linking factor present in the mammalian cell culture of step (a); and

(d) analyzing the factor for inhibition by the candidate molecule and comparing the result to the results using the control culture, wherein the candidate molecule inhibits protein:protein [linking] self-associate between factors as demonstrated by the factor being unable to mediate linking in the presence of the candidate molecule.

17. (Amended) The method of claim 15 wherein the [assay] analysis of step (d) is a gel shift assay.

18. (Amended) The method of claim 15 wherein the [assay] analysis of step (d) is a promoter activation assay.

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I hereby certify that this correspondence is being deposited with the United States Postal Services on the date set forth below as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.
Date of Signature: May 3, 1999
and Deposit: Jean C. Baker
Attorney of Record



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: William Sugden, et al.
Serial No.: 08/968,239
Filed: November 12, 1997
For: INHIBITION OF VIRAL GENE ACTIVITIES
Group Art Unit: 1643
Examiner: J. Williams

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION

Dear Sir:

1. I, William Sugden, declare that:
2. I am a named inventor on the above-identified patent application.
3. I am employed by the University of Wisconsin as a Professor of Oncology. My research interests for the past twenty-six years have been study of Epstein-Barr Virus. My curriculum vitae is attached as Exhibit A.
4. Attorney Jean C. Baker has asked me to examine the Office Action mailed December 4, 1998 in the above-identified case and comment on the Examiner's rejection of claims 8 - 10 under 35 U.S.C. § 102(b) as being anticipated by Mackey, et al. and claim 11 as being obvious over Mackey, et al. I am one of the authors of Mackey, et al. (J. Virology 69(10):6199-6208, 1995) and

the experiments described within the paper and the writing of the paper were done in my laboratory under my direction.

5. Mackey, et al. (1995) demonstrate that EBNA-1 encodes multiple domains which when fused to a protein that binds DNA site-specifically links those bound DNAs in vitro. This study does not measure DNA-linking in vivo in the presence and absence of candidate inhibitors nor is it certain that such linking could occur. DNAs in vivo are not naked nor are they freely diffusible. Rather, DNAs within nuclei in cells are likely to be bound by a complex array of proteins to form chromatin and to be compartmentalized such that local concentrations of proteins with which they interact may not be uniform.

6. Only genetic studies which can alter a protein's structure in cells by altering the gene encoding that protein could address the putative role of EBNA-1's linking domains in EBNA-1's function. Only by demonstrating that EBNA-1's linking domains and, by inference, their linking function, are required in vivo for EBNA-1's contributions to the replication and gene expression of Epstein-Barr Virus could one know that inhibition of linking would affect the function of EBNA-1.

7. This genetic analysis is provided by the present invention and the accompanying Exhibit B, Mackey

and Sugden, 1999, which reports the work of the present invention and further reduces to practice its predictions. In these studies, mutations in EBNA-1's gene that alter EBNA-1's capacity to link DNAs measured in extracts of cells *in vitro* correspondingly alter EBNA-1's ability to support replication of EBV's plasmid replicon *oriP*, *in vivo* 96 hours after its introduction into the host cells. The correlation between the ten derivatives of EBNA-1 in these two functional assays is 0.003 by the Kendall rank correlation test. Similarly the linking domains of EBNA-1 were found to be required for its support of transcription *in vivo* (Mackey and Sugden, 1999). It is the genetic analyses provided by Mackey and Sugden, 1999 and the specification of the present invention that first indicate that linking by any eukaryotic protein is likely to underlie its functional support of replication and provide the impetus to attempt to develop assays to inhibit linking in order to inhibit replication of a viral genome or to screen for inhibitors.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and

that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: 4/30/99

William Sugden
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Education:

A.B., 1967, Organic Chemistry, Harvard College, Cambridge, MA
M.S., 1968, Physical Chemistry, Columbia University, New York, NY
Ph.D., 1973, Molecular Biology, Columbia University, New York, NY

Professional Experience:

1992-present: Associate Director, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison
1985-present: Professor of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison
1980-1985: Associate Professor of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison
1975-1980: Assistant Professor of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison
1973-1975: Postdoctoral research on the molecular biology of Epstein-Barr Virus with Professor George Klein, Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden
Support: International Agency for Research on Cancer Fellowship, 1973-1974; American Cancer Society Fellowship, 1974-1975
1969-1973: Graduate work on mammalian DNA-dependent RNA polymerases and the transcription of SV40 with Dr. Joe Sambrook at the Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. Sponsored by Dr. Jim Darnell for the Ph.D. Program at Columbia University.

Honors and Professional Activities:

International Agency for Research on Cancer Fellowship, 1973-1974
American Cancer Society Fellowship, 1974-1975
American Cancer Society Faculty Research Award, 1980-1984
Chair, Oncology Fellowship Committee, 1987-present
Member of Scientific Advisory Committee, Damon Runyon-Walter Winchell Cancer Fund, 1981-1985
Member of Study Section of the American Cancer Society, 1988-1990
Member of Scientific Advisory Board, Fox Chase Cancer Institute, 1988-1990
Associate Editor, VIROLOGY, 1983-1988; 1997-present
Member, Editorial Board, CELL, 1986-1990
Member, Editorial Board, CANCER CELLS, 1989-1991
Member, Editorial Board, MOLECULAR BIOLOGY AND MEDICINE, 1986-1990

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Member, Editorial Board, MOLECULAR AND CELLULAR BIOLOGY, 1986-present
Member, Editorial Board, JOURNAL OF VIROLOGY, 1988-present
Editor, VIROLOGY, 1990-1996
Correspondent, TIBS, 1990-present
Member of Scientific Advisory Board, Tularik, San Francisco, CA, 1992-1996
James A. Miller Professor of Oncology, 1996-present
External Reviewer for Cancer Research Campaign, London, U.K., 1997-present
Member External Advisory Board of Ohio State University Comprehensive Cancer Center, 1998-present

Publications:

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Current Research Support:

- NCI P01-CA22443, Molecular Biology and Genetics of Tumor Viruses, B. Sugden (PI), Sugden subproject: Transformation of Human B-Lymphocytes by Epstein-Barr Virus; 8/17/98 to 4/30/2003 total project period; \$223,654 DC for Dr. Sugden's research for 8/17/98 to 4/30/99.
- NCI R01-CA70723, Genetic Analyses of EBV's Immortalizing Genes, B. Sugden (PI); 8/15/96 to 5/31/2001 total project period; \$175,366 DC for 6/1/98 to 5/31/99.
- Dr. Sugden is the Principal Investigator for the institutional predoctoral training grant Predoctoral Training in Experimental Oncology (CA09135); 7/1/95 to 6/30/2000 total project period; \$554,856 DC for 7/1/98 to 6/30/99 (supports 26 trainees).

U. S. Patents

- Recombinant Vector and Eukaryotic Host Transformed Thereby, granted 1987
- Lytic Origin of Replication for Epstein-Barr Virus, granted 1993
- Immortalized Lymphocytes for Production of Viral-Free Proteins, granted 1997
- Inhibition of Viral Gene Activities, Filed 11/1997

Current Campus Committee Activities:

- Chair, McArdle Fellowship Committee
- Member, McArdle Minority Recruitment Committee
- Member, McArdle Space and Program Planning Committee
- Member, Cell and Molecular Biology Program Coordinating Committee
- Member, Task Force on the Consolidation of the Cancer Centers
- Chair, Search Committee for the Howard M. Temin Professorship
- Chair, Review Committee for the UW Department of Pathology Graduate Training Program
- Member, Faculty Advising Committee, UW Medical School

Invited Research Presentations (since Fall 1990):

Fred Hutchinson Cancer Research Center, Seattle, WA, September 24, 1990
Medical College of Wisconsin, Milwaukee, WI, October 5, 1990
University of Indiana, Department of Biology, Bloomington, IN, November 1, 1990
M.D. Anderson Cancer Center, Houston, 43rd Annual Symposium on Fundamental Cancer Research, December 5, 1990
University of California-Berkeley, Department of Biology, January 31, 1991
Keystone Symposium on Molecular Biology of Human Pathogenic Viruses, Lake Tahoe, CA, March 11, 1991
Washington University, St. Louis, March 22, 1991
University of Texas, San Antonio, Department of Microbiology, April 4, 1991
Beloit Hospital, Beloit, WI (U.W. outreach program), May 15, 1991
St. Jude Children's Research Hospital, Memphis, TN, May 24, 1991
15th International Herpesvirus Workshop, Georgetown University, Washington, DC, August 4, 1991
AACR Meeting on Negative Controls on Cell Growth and their Breakdown during the Pathogenesis of Cancer, Chatham, MA, October 22, 1991
University of Kansas, Department of Microbiology, Kansas City, KS, February 27, 1992
Loyola University Medical School, Chicago, IL, June 4, 1992
Vth International Symposium of EBV, Annecy, France, September 14, 1992
Ludwig Cancer Institute, London, England, November 12, 1992
Lineberger Cancer Center, Chapel Hill, NC, February 24, 1993
University of Pittsburgh, Pittsburgh, PA, May 20-21, 1993
Pennsylvania State Medical School, Hershey, PA, June 6-11, 1993
American Society of Virology, Davis, CA, July 11-14, 1993
Northwestern University Medical School Lectures in Life Sciences, Chicago, IL, February 22, 1994
University of Utah, Department of Molecular Genetics, Salt Lake City, UT, March, 1994
Case Western Reserve University, Dept. of Biochemistry Colloquium, Cleveland, OH, April, 1994
94th General Meeting of the American Society for Microbiology, Las Vegas, NV, May 23-27, 1994
19th Intl. Herpesvirus Workshop, Keynote Address, Vancouver, BC, July 30-August 5, 1994
Howard Temin Memorial Symposium, Madison, WI, October 15, 1994
McMaster University, Hamilton, Ontario, March 2, 1995
U. Massachusetts Medical Center, Worcester, MA, March 29, 1995
Duke University Symposium on Human Tumor Viruses, April 17, 1995
Annual U.W. CMB Spring Symposium, April 22, 1995
U.W. Medical School, Department of Hematology, May 19, 1995
Tenth Annual Japanese Herpesvirus Meeting, Fuji, Japan, June 18, 1995
National Cancer Research Center, Tokyo, Japan, June 19, 1995
The Institute of Medical Science, Tokyo University, Japan, June 20, 1995
Department of Virology, Yamaguchi University, Japan, June 21, 1995
Shinogi Institute of Medical Science, Kyoto, Japan, June 23, 1995
Keystone Symposium on Viral Replication, March 5, 1996
Natl. Jewish Center for Immunology and Respiratory Medicine, Denver, CO, September 18, 1996
Hokkaido University, Sapporo, Japan, February 10, 1997
Washington University, St. Louis, MO, April 17, 1997
Hokkaido University, Sapporo, Japan, June 16, 1997
UWCCC Grand Rounds, September 10, 1997
Brockman Lecture, University of Michigan, Ann Arbor, MI, October 9, 1997
University of Iowa, Department of Microbiology, February 17, 1998
Henle Lecture, Stockholm, Sweden, June 13, 1998
23rd International Herpesvirus Workshop, York, England, August 5, 1998

Classroom Teaching (in most cases these courses are team-taught):

Bacteriology/Oncology/Plant Pathology 640 (General Virology)	1975, 1979, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998
Oncology 675 (Appropriate Conduct and Effective Communication of Science)	1996, 1997
Oncology 702	1976, 1978, 1980, 1982, 1984
Oncology 704	1977, 1979, 1981, 1983
Oncology 703 (combined 702 & 704)	1985, 1987, 1989
Neoplastic Disease (II yr, Med)	1975-1979, 1991, 1992, 1993, 1994, 1996, 1997, 1998
Grand Rounds	1978, 1979, 1997
Contemporary Biochemistry	1977
Molecular Biology Mini-course on Herpes Viruses	1976
Immunology 720	1979
Medical Microbiology 707	1977, 1979
BioCore 303	1978, 1990, 1991, 1992, 1993, 1994, 1995
Oncology course on Tumor Immunology	1978
Tumor Virology Grant Seminar, Coordinator	1975-1990
Oncology course on Human Tumor Viruses	1986
Neurochemistry 611	1988
Pathology 404	1999